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Asymmetric Synthesis of Dihydropyranones with Three Contiguous Stereocenters by an NHC-Catalyzed Kinetic Resolution

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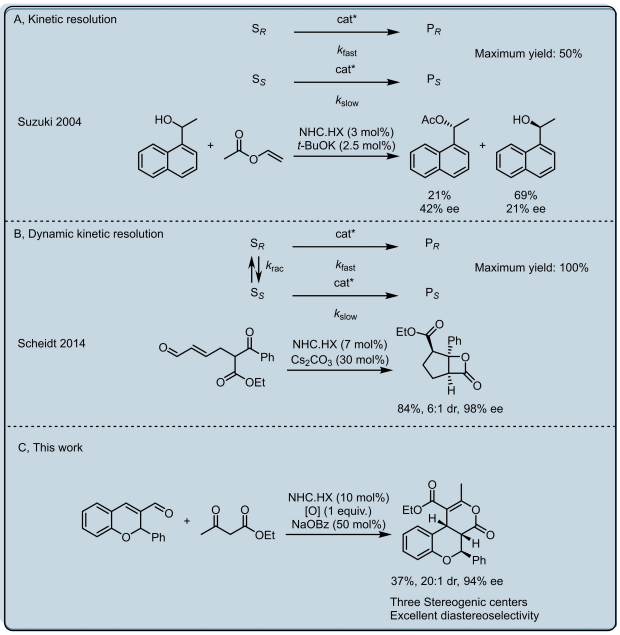
An oxidative NHC-catalyzed kinetic resolution (KR) of racemic mixtures is presented. The developed reaction furnishes tricyclic dihydropyranones with three contiguous stereocenters in excellent dia- and enantioselectivity, with good-to-moderate yields. Mechanistic studies indicate that the rate-determining step of the reaction is the formation of the Breslow intermediate, while the selectivity determining step occurs later in the mechanism. The presented methodology enables rapid synthesis of complex structures in a single step.

Synthesis of enantioenriched materials is central to organic chemistry. A common strategy for accessing enantioenriched products is to use an enantioselective catalyst to resolve racemic mixtures. The first report of this strategy dates back to 1858 when Pasteur reported the enzymatic kinetic resolution of tartaric acid.[1] Since then, resolution of racemic mixtures has become an important field that has grown tremendously and a wide range of methods have been reported.[2]

N-heterocyclic carbenes (NHCs) have gained widespread attention as effective organocatalysts for an impressive range of transformations.[3] Lately, they have also proved effective catalysts for resolution of racemic mixtures.[4] Suzuki *et al.* reported the first NHC-catalyzed resolution, an enantioselective acylation of secondary alcohols with vinyl acetate via a kinetic resolution (KR) strategy (Scheme 1A).[5] In a kinetic resolution, a chiral reagent is used to distinguish between the two enantiomers by a difference in reaction rate, leading to enantioenriched materials. NHC-catalyzed kinetic resolutions have proven to be a powerful tool and have been applied to a wide range of substrates including sulfoximines,[6] azomethine imines,[7] secondary amines,[8] axially chiral diols,[9] and formyl β-lactams.[10] Kinetic resolutions have an intrinsic limitation to a maximum yield of 50%. However, in dynamic kinetic resolutions (DKRs) the two enantiomers rapidly interconvert, and a maximum yield of 100% is possible (Scheme 1B). A prerequisite for a successful DKR is that the rate of racemization of the substrate is significantly higher than the rate of reaction for the slow reacting isomer ($k_{rac} \gg k_{slow}$). In DKRs, the interconversion is often based on either deprotonation of labile protons or redox racemization.[11] For example, in 2014 Scheidt and co-workers reported an NHC-catalyzed DKR, in the synthesis of bicyclic β-lactones from enals containing a 1,3- dicarbonyl moiety.[12]



Scheme 1. NHC-catalyzed resolutions of racemic mixtures.

Since then, NHCs have been used for the DKR of α-ketoesters,[13] 6-hydroxypyranones[14] and ketoacids.[15]

Here, we present a method for the asymmetric synthesis of chroman-substituted dihydropyranones with three contiguous stereocenters by an NHC-catalyzed KR (Scheme 1C).

Initially, we wished to investigate how chromanaldehydes such as **1** behaved in the NHC-catalyzed oxidative cyclization

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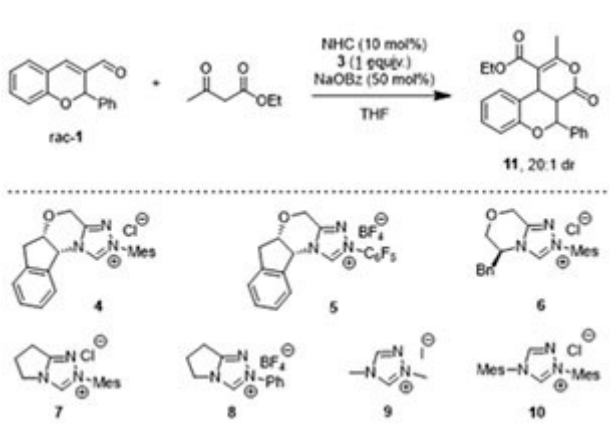
with 1,3-dicarbonyls (Scheme 2), as first reported by Studer and co-workers.[16] Chromane is a privileged scaffold in medicinal chemistry,[17] and several drugs and bioactive natural products contain a tricyclic chromane core as found in **2**, for instance nabilone,[18] tetrahydrocannabinol[19] and the ohioensins.[20] α,β-Disubstituted enals are known to give dihydropyranones in poor diastereoselectivity,[16] which inspired Xu *et al.* to design a new NHC-catalyst that displayed moderate to good diastereoselectivity.[21] Furthermore, Biju and co-workers have shown that coumarins are an excellent substrate for the synthesis of tricyclic dihydropyranones.[22] However, there are no reports on the effect of cyclic enals or the presence of an existing stereocenter in the annulation.

When *rac*-**1** and benzyl acetoacetate was treated with NHC **4**, oxidant **3** and sodium acetate in THF, the tricyclic dihydropyranone **2** was isolated in 14% yield and exquisite diastereoselectivity (Scheme 2A). A measurement of the optical rotation confirmed that the reaction is in fact a kind of resolution ($[\alpha]_D^{20} = 103^\circ$). When (*R*)-**1** was reacted under the same reaction conditions with either **4** (Scheme 2B) or *ent*-**4** (Scheme 2C), the product **2** formed in the former case (26% yield) but not in the latter. The product obtained from (*R*)-**1** exhibited similar optical rotation as the one obtained using *rac*-**1** ($[\alpha]_D^{20} = 106^\circ$ *vs.* $[\alpha]_D^{20} = 103^\circ$) which confirmed that the reaction is a resolution and that the stereochemistry of C9 **2** is *S*.

With a greater understanding of the reaction, an optimization process was initiated (Table 1). Due to simpler purification, the optimization was performed using ethyl acetoacetate and not benzyl acetoacetate. Using the standard conditions dihydropyranone **11** was formed in 23% yield and 98:2 er, with maintained exquisite diastereoselectivity. One of the other main products of the reaction is an unstable acyclic enol ester of the acetoacetate that could be isolated in 5% yield (see Supporting Information). The reaction proved highly sensitive to the choice of NHC catalyst, of the investigated precatalyst only **4** proved capable of yielding **11** (Table 1, entry 2). The reaction was then performed using 0.5 equiv. of oxidant **3** to gain further information of how the resolution proceeds (Table 1, entry 3). The reaction yielded **11** in 15% yield with maintained enantioselectivity together with 50% of aldehyde **1**. Surprisingly, the er of the isolated aldehyde was 55:45 favoring the *R*-enantiomer, meaning that the enantiomer which yields the dihydropyranone actually reacts slower than its antipode. Moreover, this experiment told us that the resolution occurs after the oxidation step in the mechanistic cycle. A wide range of bases was screened (optimization in Supporting Information). Using the stronger base Cs_2CO_3 gave a similar yield as NaOAc but with slightly reduced enantioselectivity. The organic base DABCO gave **11** in 35% yield and 95:5 er. The best results were obtained using sodium benzoate (NaOBz), which yielded **11** in 37% yield and 97:3 er. A solvent screen showed that PhMe, dioxane and DCM were unsuitable as reaction solvents, giving **11** in very low yields (Table 1, entry 8–10). Using EtOAc, **11** was obtained in 31% yield and 98:2 er (Table 1, entry 11).

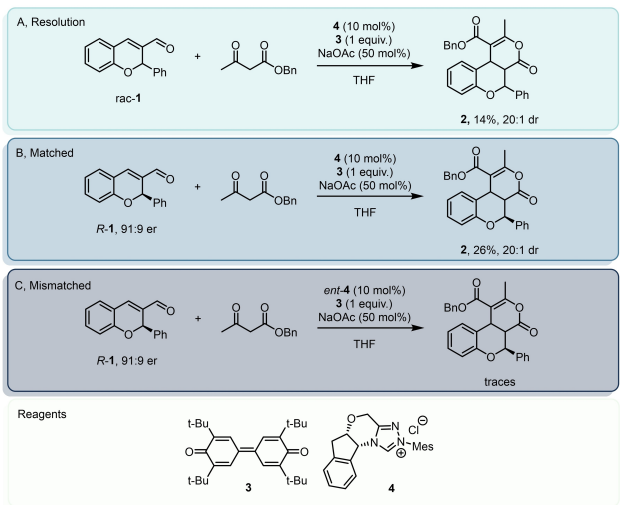
With methyl *tert*-butyl ether (MTBE) as reaction solvent, the yield was reduced and the enantioselectivity maintained as compared to THF (Table 1, entry 12). Performing the reaction at 0 °C instead of room temperature resulted in a significantly reduced reaction rate and only slightly increased enantioselec-

Table 1. Optimization of reaction conditions.[a]



Entry	NHC	Base	Solvent	Yield[b]	er
1	**4**	NaOAc	THF	23%	98:2
2	**5-10**	NaOAc	THF	0%	–
3[c]	**4**	NaOAc	THF	15%	98:2
4	**4**	Cs_2CO_3	THF	24%	97:3
5	**4**	DBU	THF	22%	92:8
6	**4**	DABCO	THF	35%	95:5
7	**4**	**NaOBz**	**THF**	**37%**[d]	**97:3**
8	**4**	NaOBz	PhMe	0%	–
9	**4**	NaOBz	Dioxane	8%	–
10	**4**	NaOBz	DCM	5%	–
11	**4**	NaOBz	EtOAc	31%	98:2
12	**4**	NaOBz	MTBE	24%	97:3
13[e]	**4**	NaOBz	THF	24%	98:2
14[f]	**4**	NaOBz	THF	15%	97:3

[a] **1** (1 equiv.), ethyl acetoacetate (1 equiv.), solvent (0.1 M), performed at rt for 24 h. [b] Determined by ^{1}H NMR using DMF as an internal standard. [c] Using 0.5 equiv. of **3**.[d] Isolated yield. [e] Performed at 0 °C for 48 h. [f] Performed using 2 equiv. of ethyl acetoacetate.



Scheme 2. Initial results for the NHC-catalyzed synthesis of dihydropyranones by resolution.

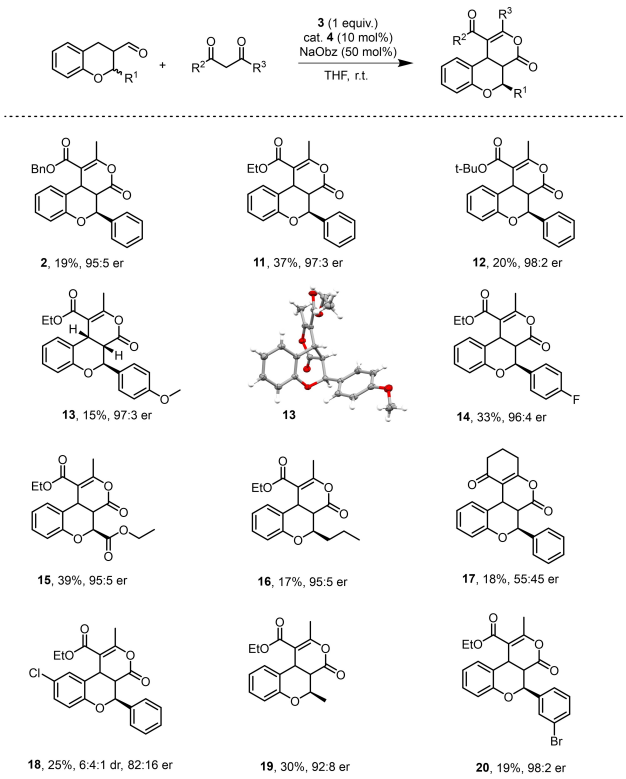
tivity, yielding **11** in 24% and 98:2 er. A wide range of different stoichiometries and different additives such as Lewis acids, proton shuttles and crown ethers were also screened, but no change from entry 7 proved beneficial. For instance, using 2 equiv. of ethyl acetoacetate yielded **11** in 15% yield and 97:3 er. The lack of complete mass balance can be explained by parasitic side reactions, one being the enol ester of the acetoacetate and the other one a Knoevenagel condensation.

With an optimized procedure in hand, we continued to evaluate the scope of this kinetic resolution (Scheme 3). Using other ketoesters than ethyl acetoacetate gave lower yields but with a maintained high enantioselectivity, for instance product **2** and **12** that were isolated in 19% yield and in 95:5 er and 20% yield and in 98:2 respectively. Crystal structure elucidation of product **13** revealed the relative stereochemistry of the three consecutive stereocenters. The hydrogens of the chiral centers, C8 and C23, and the pending phenyl moiety are *syn* to one another. Chromenaldehydes with electron poor aryl substituents at C9 give higher yields than the electron rich counterparts, with consistently high enantioselectivity. For instance, fluorinated dihydropyranone **14** was isolated in 33% yield and 96:4 er. Ester substituted chromenaldehydes can also be used as substrates in the KR and diester **15** could be isolated in 39% yield and 95:5 er. Furthermore, alkyl substituted chromenaldehydes are well tolerated by the reaction affording **16** and **19** in 95:5 and 92:8 er, respectively. Using cyclohexan-1,3-dione as the nucleophile in the reaction gave tetracyclic dihydropyranone **17** in 18% yield as an almost racemic mixture, 55:45 er. The reason for the dramatic drop in selectivity with cyclohexan-1,3-dione is not currently understood, but similar effects have been previously observed.[23] Another surprising result was obtained using a chromenaldehyde with a chloro-substituent. This resulted in dihydropyranone **18**, where the chloro is bound to C20, in a 25% yield with an 82:18 er, and 6:4:1 dr. This is the first instance where any trace of another diastereomer was observed.

In order to probe the mechanism of dihydropyranone formation, kinetic studies were performed using gas chromatograph equipped with a flame ionization detector (GC-FID) (see Supporting Information). This revealed that the global reaction order for this KR is one (Figure 1).

A reaction order of one means that the rate determining step (RDS) cannot involve more than one molecule of either aldehyde, oxidant or ethyl acetoacetate since this would result in a reaction order higher than one. The generally accepted mechanism for dihydropyranone formation is seen in Scheme 4.[14] Potentially, there are three different processes that could be the rate determining step. This could be either: (1) nucleophilic addition of carbene ***I*** to the aldehyde to yield ***III***, (2) formation of the Breslow intermediate ***IV*** from the tetrahedral intermediate, or (3) deprotonation of ethyl acetoacetate to yield ***VI***.

The observation that the rate did not change significantly when using DABCO instead of NaOBz suggests that the deprotonation of ethyl acetoacetate is not rate determining since DABCO is a weaker base (pK_a 8.9 *vs.* 11.1 in DMSO)[24] assuming similar RDS in both cases. Several computational studies have shown that the formation of ***III*** is more facile than the subsequent proton transfer to yield the Breslow intermediate ***IV***.[25] Smith *et al.* have reported that the formation of the Breslow intermediate is three to four orders of magnitude slower than the formation of the tetrahedral intermediate for a



Scheme 3. Scope of the kinetic resolution.

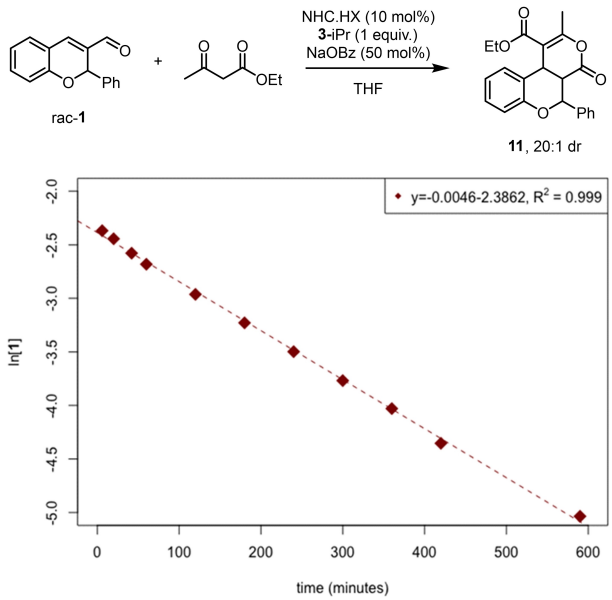
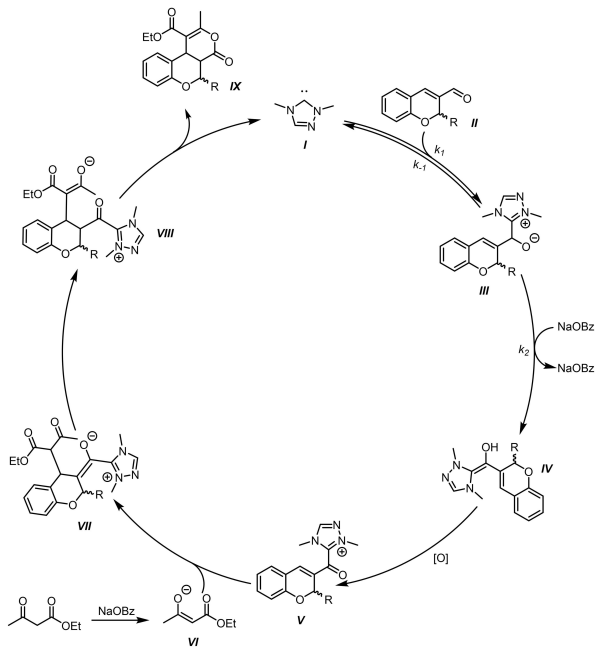


Figure 1. Determination of reaction order with respect to **1**. The overall reaction order for this KR is one.



Scheme 4. Proposed mechanism for dihydropyranone formation.

range of substituted benzaldehydes.[26] In light of this, we propose that the RDS of this transformation is the formation of the Breslow intermediate ***IV***. As the RDS lies before any of the selectivity determining steps, these cannot be probed by kinetic studies.

Conclusion

The developed methodology enables rapid access to structurally complex dihydropyranones containing three consecutive stereocenters. The reaction is characterized by high levels of diastereoselectivity and enantioselectivity, with moderate to good yields. Kinetic experiments showed that the reaction follows an overall first reaction order, which supports the formation of the Breslow intermediate as the rate determining step. However, the selectivity determining step lies after the oxidation event, which hinders further interrogation by kinetic measurements. The presented methodology showcases the potential of NHC-catalyzed resolution of racemic mixture via complexity generating reactions.

Author Contributions

All authors have given approval to the final version of the manuscript.

Notes

The Authors declare no competing financial interest.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Organocatalysis · Oxidative NHC · NHC · Structurally divergent resolution

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